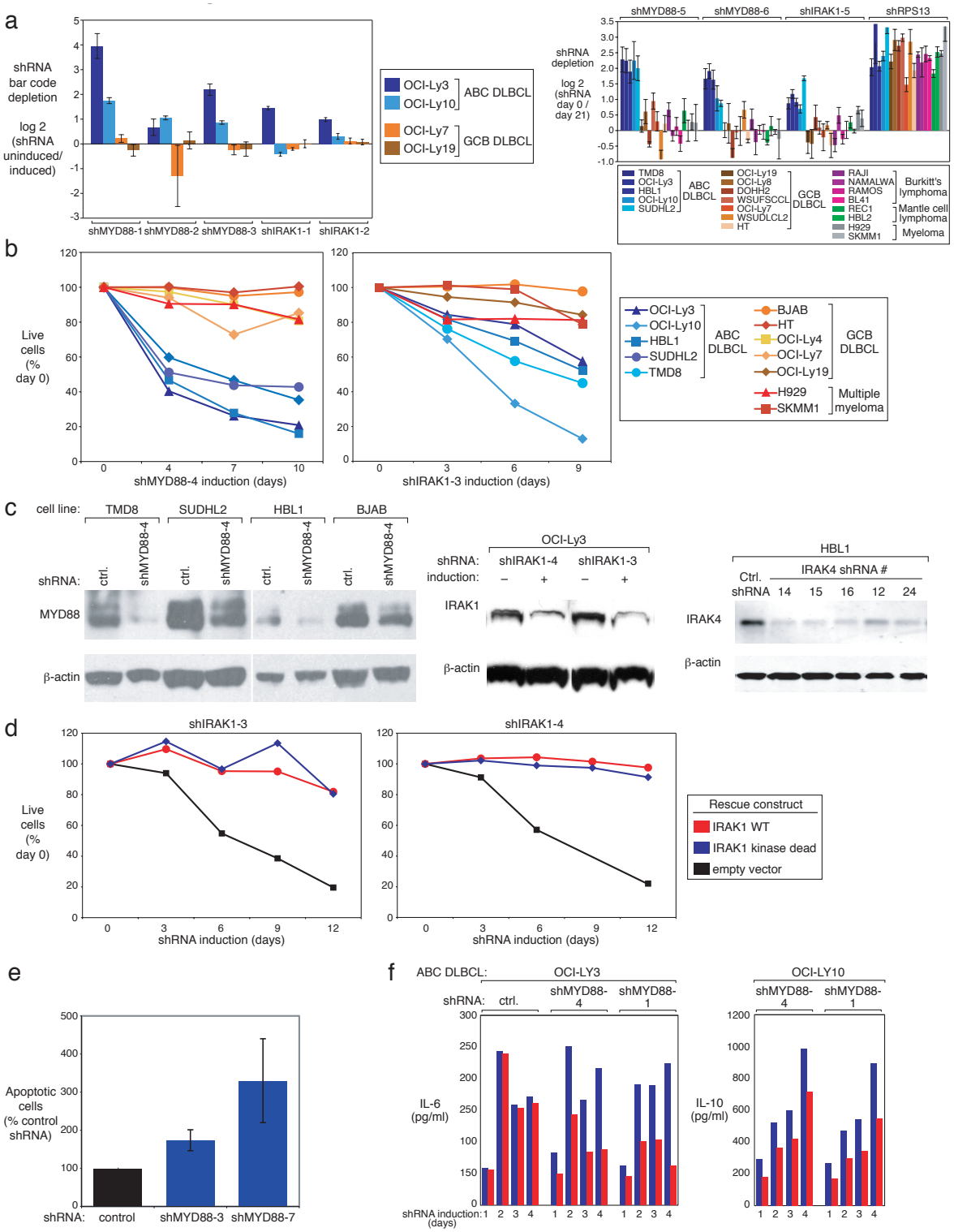
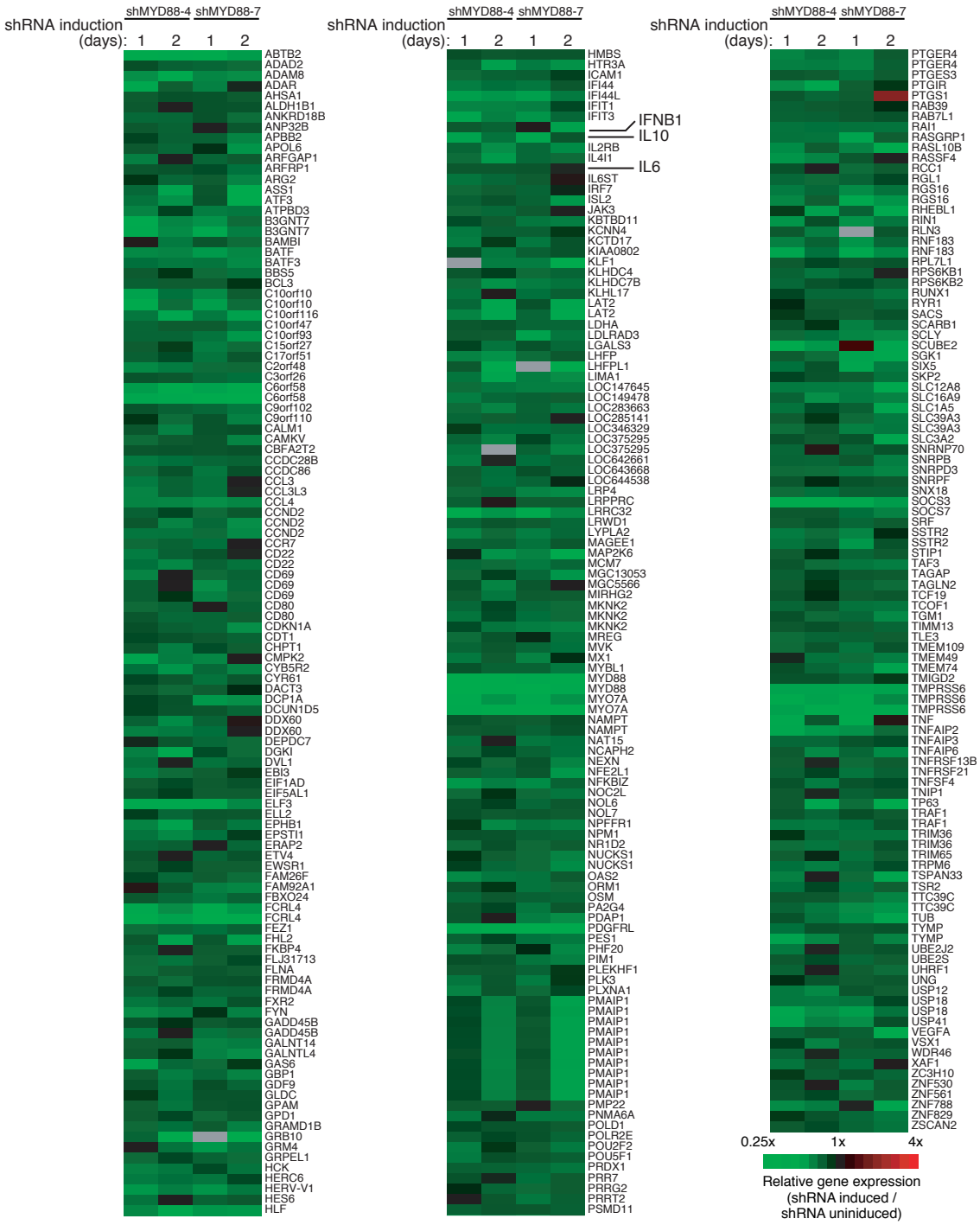
doi:10.1038/nature09671

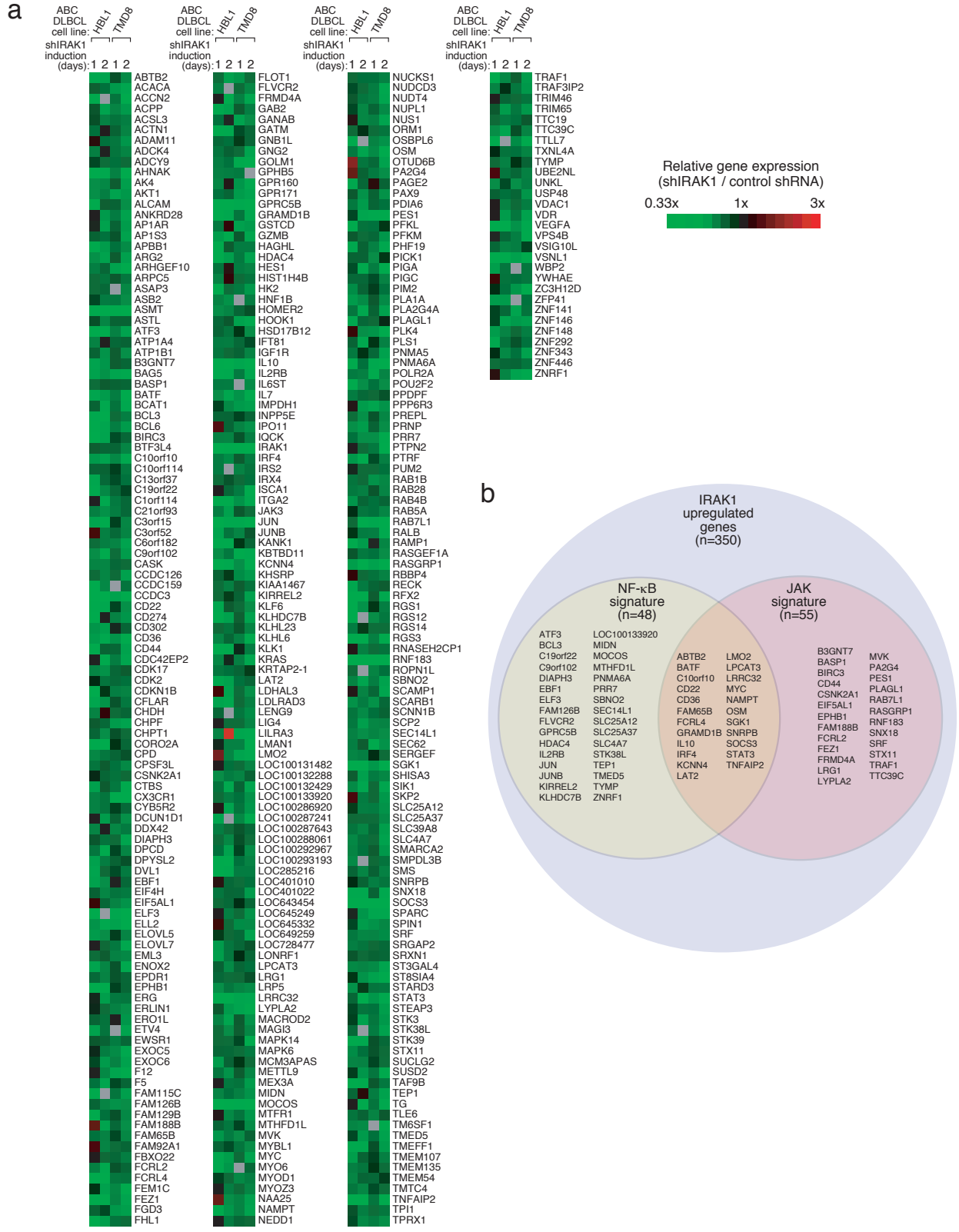


Supplementary Figure 1. Validation of MYD88 and IRAK1 shRNAs. a, An RNA interference screen identified shRNAs targeting MYD88 and IRAK1 as toxic for ABC

DLBCL lines. Left panel: the indicated lymphoma lines were transduced with an shRNA library targeting 1165 genes as described[1]. After 21 days in culture, shRNA abundance was compared between cell populations in which shRNA expression was induced or left uninduced. Right panel: The indicated lines were transduced with a focused library containing shRNAs targeting *MYD88*, *IRAK1* and the positive control *RPS13*. shRNA abundance was compared between cells prior to shRNA induction and after 21 days of shRNA induction. Error bars are s.e.m. (n=4). **b,** Selective toxicity of MYD88 and IRAK1 shRNAs for ABC DLBCL lines. The fraction of GFP+, shRNA-expressing cells relative to the GFP–, shRNA-negative fraction at the indicated times is plotted, normalized to the day 0 values. **c,** left panel: knockdown of MYD88 protein by shMYD88-4 relative to a control (ctrl.) shRNA confirmed by immunoblotting using the indicated cell lines; middle panel: knockdown of IRAK1 protein by doxycycline-induced expression of two IRAK1 shRNAs relative to uninduced OCI-Ly3 ABC DLBCL cells confirmed by immunoblotting; right panel: knockdown of IRAK4 protein by doxycycline-induced expression of 5 IRAK4 shRNAs in HBL1 ABC DLBCL cells, compared to HBL1 cells induced to express a control (ctrl.) shRNA. **d,** Rescue of shIRAK1 toxicity by wild type and kinase dead IRAK1 coding region cDNAs. The ABC DLBCL cell line HBL1was transduced with an inducible shRNA targeting the 3' UTR of the IRAK1 mRNA and subsequently transduced with rescue constructs expressing the coding regions of wild-type or kinase-dead IRAK1. Shown is the fraction of GFP+, shRNA-expressing cells relative to the GFP–, shRNA-negative fraction at the indicated times, normalized to the day 0 values. Data are representative of 3 independent experiments. **e,** Induction of apoptosis by MYD88 knockdown in ABC DLBCL cells. HBL1 ABC DLBCL cells were transduced with the indicated MYD88 shRNA vectors and the number of apoptotic cells was measured by FACS. Shown is the average fold increase in apoptotic cells relative to HBL1 cells transduced with a control shRNA, based on 2-5 measurements. Error bars are s.e.m. (n=2-5). **f,** MYD88 promotes IL-6 and IL-10 secretion in ABC DLBCL. MYD88 or control shRNAs were induced in the indicated ABC DLBCL lines for various times and supernatants were assayed for IL-6 or IL-10.



Supplementary Figure 2. MYD88 responsive genes in the HBL1 ABC DBLCL cell line. Expression of shMYD88-4 or shMYD88-7 was induced for the indicated times in HBL1 cells. Gene expression profiling was used to identify genes that depend upon MYD88 signaling. Relative gene expression in induced versus uninduced cells is displayed according to the color scale shown.



Supplementary Figure 3. IRAK1 responsive genes in ABC DLBCL.

a, The indicated ABC DLBCL cell lines were induced to express an IRAK1 shRNA or a control shRNA for 24 or 48 hours. Relative expression of genes in shIRAK1 vs. control shRNA-transduced cells is depicted according to the color scale shown.

1 **Milhollen, M. A. *et al.* MLN4924, a NEDD8-activating enzyme inhibitor, is active in diffuse large B-cell lymphoma models: rationale for treatment of NF-{kappa}B-dependent lymphoma. *Blood* 116, 1515-1523 (2010).**